REMARKS

Reconsideration and withdrawal of the rejection in the outstanding Office Action are respectfully requested in view of the foregoing amendments and the following remarks.

Summary of Status of Amendments and Office Action

In the present amendment, claims 1, 6, 7, 13, 15, 18, and 19 are amended. Claims 5 and 17 are canceled. Therefore, claims 1-3, 6-15, and 18-24 are pending in the application, with claims 1 and 13 being independent.

Applicants have amended the claims to more clearly recite the claimed subject matter. Support for the amendments are found in the application as filed. Applicants have amended claims 6 and 7 to maintain proper claim dependency. No new matter is added.

Allowable Subject Matter

Applicants acknowledge the Office's indication that claims 6-7 would be allowable if rewritten to overcome the rejections under 35 U.S.C. § 112, second paragraph, as discussed below, and to include all of the limitations of the base claim and any intervening claims. Also, claims 18-19 are asserted by the Office to be allowable if rewritten in independent form including all of the limitations of the base claim and intervening claims.

Response to Claim Objections

Claims 1-3 and 4-12 are objected because the rejection asserts that the words "hydrogentaed" in claim 1, "polyysorbate" in claim 19, and phrase "one of" in claim 7 may be typographical errors. In response, Applicants have amended the claims to correct these typographical errors.

Response to 112, second paragraph Rejections

Claims 1-3 and 4-12 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to point out and distinctly claim the subject matter. The rejection asserts that claims 1-3 and 4-12 are vague and indefinite because the preamble recites a process for preparing a powder containing the physiologically active peptide, but there is allegedly no active step for preparing a powder containing the physiologically active peptide.

In response, Applicants respectfully submit that the claims pending prior to the present amendment definitely define what Applicants consider to be their invention. However, in order to advance prosecution of the present application, and without acquiescence, Applicants have amended claim 1 to recite a method of stabilization of a physiologically active peptide in a process of preparing a powder containing the physiologically active peptide, wherein the process comprises drying an aqueous liquid containing the physiologically active peptide to form a powder.

Additionally, Applicants have amended claim 13 to include a recitation wherein the method comprises adding to the aqueous liquid containing the physiologically active peptide at least one compound selected from the group of a water-soluble, nonionic, organic binder, and hydrogenated lecithin, wherein the nonionic, organic, water-soluble binder is selected from polyvinylpyrrolidone, a water-soluble, nonionic cellulose derivative, and polyvinylalcohol, and wherein the method comprises drying the liquid to form a powder.

Reconsideration and withdrawal of these rejections is respectfully requested.

Response to 103(a) Rejection

Claims 1-3, 5, 8-15, 17, and 20-24 are rejected under 35 U.S.C. § 103(a) as being unpatentable over U.S. Patent No. 6,103,697 to Bergstrand et al. ("Bergstrand") further in view of U.S. Patent No. 6,117,434 to Oyama et al. ("Oyama").

According to the Office, Bergstrand discloses the preparation of a pharmaceutical preparation containing a peptide and that the active peptide may be admixed with mannitol, cellulose derivatives, or polyvinylpyrrolidone, as well as surfactants, such as lecithin. The Office admits that Bergstrand does not disclose the amount of nonionic surfactant, a nonionic, organic, water-soluble binder and mannitol used. However, the rejection alleges that it would have been prima facie obvious to select the specific ratio of weight to these compounds used in the method for preparing

a powder for containing a physiological active peptide, because the selection is routine optimization with regard to sequence, length and amount of compounds used.

Additionally, the rejection asserts that even though Bergstrand does not disclose hydrogenated lecithin, Oyama discloses hydrogenated lecithin in a moisturizing composition with oxidation stability. The rejection asserts that one of ordinary skill in the art would have been motivated to add hydrogenated lecithin in an aqueous solution containing active peptide because of the oxidation stability of hydrogenated lecithin taught by Oyama. Applicants respectfully disagree and traverse the rejection as follows.

In order to establish a prima facie case of obviousness, the Office must meet three criteria: (1) that the combination of references teach or suggest to the ordinary skilled artisan all of the recited claim limitations; (2) that there must be motivation in the cited art to combine the references to devise the claimed invention; and (3) there must be a reasonable expectation of success of successfully practicing the invention. *See* M.P.E.P. § 2143. In the present case, the Office has failed to make a *prima facie* case of obviousness because it has not met any, let alone all three of the above criteria.

Combination of Documents Does Not Teach or Suggest All Claim Recitations

Applicants note that Bergstrand is directed to a method of preparing peptides with cysteine-containing motifs having an immunostimulating or immunoinhibitory effect. Applicants point out that the lyophilization described in Bergstrand (Example 34, column 9, lines 58-60) is the first step of purification of a peptide synthesized from monomers. Applicants submit that the lyophilized peptide is not a pharmaceutical preparation but simply a transient form which is then subjected to further purification steps including HPLC after a solvent exchange (redissolution in water/acetonitrile). There is no disclosure in Bergstrand regarding the stability of the peptide in the lyophilization step. In addition, Applicants note that Bergstrand discloses immunomodulator peptides, and Applicants do not see a reference to growth hormone at column 2, lines 15-20, as alleged by the Office.

The disclosure at col. 12, lines 56-65, teaches admixing the peptide with an adjuvant or carrier, such as, mannitol, cellulose derivatives, polyvinylpyrrolidone, and then compressing the mixture into tablets. This disclosure suggests admixing the adjuvant or carrier with the peptide in powder form and then compressing the mixture into tablets. Similarly, the disclosure at col. 13, lines 53-64, teaches adding low concentrations of surfactants such as lecithin, solvents, or other additives to the peptide powder formulation. There is no teaching or suggestion that the surfactants or other additives are added to physiologically active peptide in aqueous solution, to stabilize a physiologically active peptide during drying, and then dried to form a powder. Moreover, there is no teaching or suggestion in Bergstrand of a method of

stabilization of a physiologically active peptide in a process of preparing a powder by drying an aqueous solution of a peptide while increasing the stability of the peptide by adding at least one compound selected from polyvinylpyrrolidone, water-soluble, nonionic cellulose derivatives, polyvinylalcohol, and hydrogenated lecithin to the solution. Accordingly, the claims are not obvious because Bergstrand does not teach or suggest all of the recited claim limitations.

The combination of Bergstrand and Oyama does not correct this deficiency. Oyama is directed to a "moisturizing composition" comprising a trihydric or more water soluble polyhydric alcohol, lecithin and 3-methyl-1,3-butylene glycol. Oyama describes a moisturizing composition such as skin lotion (Example 27), cleansing type cosmetics (Example 28), cream (Example 29), liquid cream (Example 30), cleansing gel (Example 33), and moisture gel (Example 34) and pack (Example 35). The compositions of Oyama are not powder compositions, but wet compositions.

Even if such a combination is contemplated, the combination of Bergstrand and Oyama still do not teach or suggest to one of ordinary skill in the art a method of stabilization of a physiologically active peptide in a process of preparing a powder by drying an aqueous solution of a peptide while increasing the stability of the peptide by adding water-soluble, nonionic, organic binder and/or hydrogenated lecithin to the solution. Further, there is no teaching or suggestion that Oyama's moisturizing compositions can be prepared as powder compositions, or would be useful in powder form for stabilizing a physiologically active peptide.

Accordingly, the claims are not obvious because the combination of Bergstrand and Oyama do not teach or suggest all of the recited claim limitations.

No Motivation to Modify or Combine the References

There is no motivation in the cited documents for the ordinary skilled artisan to combine or modify the references to devise the claimed invention. The rejection alleges that it would have been prima facie obvious to modify Bergstrand to select the specific ratio of weight to these compounds used in the method for preparing a powder for containing a physiological active peptide, because the selection is routine optimization with regard to sequence, length and amount of compounds used.

Bergstrand's lyophilized peptide is not a pharmaceutical preparation but simply a transient form which is then subjected to further purification steps including HPLC after a solvent exchange (redissolution in water/acetonitrile). Unlike Bergstrand, the claimed invention is not directed towards methods of lyophilizing peptides in general, but rather a method of stabilization of a physiologically active peptide in a process of preparing a powder containing the physiologically active peptide. It would be understood by those of ordinary skill in the art that not all lyophilized peptides, particularly Bergstrand's lyophilized peptide, would be stabilized as a result of preparing a physiologically active peptide by drying an aqueous liquid containing the physiologically active peptide to form a powder, wherein the method comprises adding to the aqueous liquid at least one compound selected from the group of a nonionic, organic, water soluble binder, and hydrogenated lecithin, and wherein the nonionic, organic, water-soluble binder is selected from polyvinylpyrrolidone, a water-soluble, nonionic cellulose derivative, and polyvinylalcohol. Indeed, Bergstrand teaches adding additives to the powder

formulation. Col. 13, lines 62-64. One of skill in the art reading Bergstrand would understand that Bergstrand is suggesting that additives, such as surfactants and solvents, be added to their peptide powder.

Furthermore, Applicants submit that the Office has not provided clear and particular evidence that teaches or suggests that one of ordinary skill in the art would have been motivated to use the hydrogenated lecithin of Oyama's moisturizing compositions in the lyophilized peptide powder of Bergstrand. Oyama's moisturizing composition requires the combination of three moisturizing components to attain the disclosed moisturizing and stability characteristics: a trihydric or polyhydric alcohol, lecithin, and 3-methyl-1,3-butylene glycol at specific weight ratios. Col. 2, lines 2-8. The Office asserts that the motivation for using Oyama's moisturizing hydrogenated lecithin in Bergstrand's lyophilization method comes from the desirable oxidation stability of the hydrogenated lecithin. First, Oyama's other components the trihydric alcohol and glycol compound are required to attain the stability achieved by Oyama. There is no evidence that one of ordinary skill in the art would selectively pick and choose only hydrogenated lecithin from the various components required to achieve Oyama's moisturizing stability. Second, Oyama involves the art of moisturizing compositions wherein the moisturizing agents "play an important role to work as an agent retaining the moisture of cosmetics or external preparations themselves and thereby contribute to the retention of the stability of the system." Col. 1, lines 27-30. Thus, Oyama's mention of hydrogenated lecithin's increasing oxidation stability relates

to Oyama's goal of attaining stability of a moisturizing composition which includes stability in retaining moisture. There is no suggestion in the cited documents that lyophilized powders function as moisturizing compositions. Accordingly, one of ordinary skill in the art would not be motivated to combine Oyama's moisturizing agents with the Bergstrand's lyophilization method. The use of hydrogen lecithin in a method of stabilization of a physiologically active peptide in a process of preparing a powder by drying an aqueous liquid containing the active peptide and hydrogen lecithin is suggested only in the Applicant's specification.

Furthermore, Bergstrand neither teaches nor suggests a method of stabilization of a physiologically active peptide in a process of preparing a powder. In contrast to Bergstrand which disclose a method of admixing mannitol, cellulose derivatives, or polyvinylpyrrolidone with a peptide and then compressing to make tablets, the present invention claims methods of making a powder by drying a liquid. Thus, the evidence relied upon by the Office does not provide the requisite motivation for one of ordinary skill in the art to devise the Office's proposed modification of Bergstrand or its combination with Oyama.

No Reasonable Expectation of Success

Furthermore, there is no evidence of record that indicates that one of ordinary skill in the art at the time of filing would have had a reasonable expectation of success of modifying or combining the cited references to devise the claimed method. For

example, there is no reasonable expectation of success of modifying Bergstrand's lyophilization process to stabilize Bergstrand's peptide in a process of preparing a powder containing the physiologically active peptide by drying an aqueous liquid comprising at least one compound selected from hydrogenated lecithin, polyvinylpyrrolidone, water-soluble, nonionic cellulose derivatives, and polyvinylalcohol, because there is no teaching or suggestion that Bergstrand's lyophilized peptide at example 34, lines 58-60, is stabilized.

In addition, Oyama's moisturizing composition requires the combination of three moisturizing components to attain the sought after moisturizing stability. Oyama teaches that hydrogenated lecithin must be used in combination with other specific moisturizing agents in order to achieve the sought after stabilized moisturizing composition. Thus, there is no reasonable expectation that one of ordinary skill in the art at the time of filing would successfully pick and choose one of those moisturizing agents (e.g. hydrogenated lecithin) and combine it with Bergstrand's lyophilization method to successfully devise the claimed method of preparing a stabilized peptide in powder form.

For any one of the above reasons, Applicants respectfully submit that they have traversed the rejections under 35 U.S.C. § 103(a), and respectfully request that the Office withdraw the rejections of claims 1-3, 5, 8-15, 17, and 20-24.

CONCLUSION

For the foregoing reasons, it is believed that all of the claims in this application are in condition for allowance, which action is respectfully requested.

If the Examiner has any questions, or wishes to discuss this matter, the Examiner is respectfully invited to contact the undersigned at the below-listed telephone number.

Respectfully submitted,
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